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(19)(CA) **CANADIAN PATENT** (12)

(54) Use of Ethylene Oxide/Propylene Oxide Block Copolymers for Controlling Foam in Liquid Pharmaceutical Formulations, Pharmaceutical Formulations, and a Process for their Preparation

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Abstract of the disclosure

The use of ethylene oxide/propylene oxide block copolymers for controlling foam in pharmaceutical formulations, especially in those for parenteral administration, is described. Also described are liquid pharmaceutical formulations and a process for their preparation.

HOECHST AKTIENGESELLSCHAFT Dr.D/gm HOE 86/F 121

The use of ethylene oxide/propylene oxide block copolymers for controlling foam in liquid pharmaceutical formulations, pharmaceutical formulations, and a process for their preparation

The preparation and dispensing of liquid pharmaceutical formulations for parenteral administration which are prone to foam-formation are difficult and always time-consuming. There is also delay involved in preparation for administration since it is necessary to await the collapse of the foam.
An injection solution whose surface is covered with foam cannot be administered.

For toxicological reasons, there are problems with customary antifoam agents for liquid pharmaceutical formulations for oral administration, such as silicone oil or octanol, as additives to formulations for parenteral use. In addition, these additives may cause turbidity in injection solutions. It has been found, surprisingly, that traces of a surfactant of the ethylene oxide/propylene oxide block copolymer type effect rapid collapse of the foam.

Ethylene oxide/propylene oxide block copolymers are used as weakly foaming raw materials in detergents for dishwashing and laundering. Their properties as emulsifiers, demulsifiers and wetting agents have been described. However, the possibility of using them as antifoam agents is unknown.

Thus the invention relates to the use of ethylene oxide/propylene oxide block copolymers for controlling foam in liquid pharmaceutical formulations, especially in those for parenteral administration.

The particularly preferred ethylene oxide/propylene oxide block copolymer is polyethylene/polypropylene glycol 1800 -

(also called PPG 1800). The use in formulations for parenteral administration is particularly preferred. The antifoam agent must comply with the purity criteria normally required of pharmaceutical auxiliaries.

In principle, the ethylene oxide/propylene oxide block copolymers are suitable for controlling foam in all liquid formulations, especially aqueous, of pharmaceuticals. Of course, the medicinal agents must be compatible with the ethylene oxide/propylene oxide block copolymers used. Examples of suitable medicinal agents are cephalosporin derivatives such as cefpirom (HR 810) and penicillin derivatives such as procaine benzylpenicillin.

The invention also relates to pharmaceutical formulations containing ethylene oxide/propylene oxide block copolymers for controlling foam, and to a process for their preparation.

The liquid formulation contains about 0.1 to 0.00001% by weight of ethylene oxide/propylene oxide block copolymer such as, for example, PPG 1800, preferably 0.01-0.0001% by weight of PPG 1800.

The process for the preparation of the formulations comprises application of ethylene oxide/propylene oxide block copolymers to the solid active compound, or impregnation of the latter with the polymer or addition of the polymer to the solvent.

Example 1

A formulation intended for injections and containing 1.23 g of HR 810 sulfate and 0.22 g of Na_2CO_3 (anhydrous) showed, after dissolution in 10 ml of water, a foam which was stable for about 5 minutes.

If a 0.0005% strength aqueous solution of polyethylene/polypropylene glycol 1800 is used instead of water for

dissolving, the foam collapses virtually immediately after the dissolution.

The same effect can be achieved if approximately equivalent amounts of PPG 1800 are applied to the solid components, singly or altogether, for example by precipitation in the presence of PPG 1800, by addition of PPG 1800 to the solution used for washing the precipitated solids, or by spraying PPG 1800 solution onto the solids, followed by drying. It is also possible to achieve the antifoam effect of PPG 1800 by impregnation of the primary packaging (for example injection vials and/or injection vial stoppers) with PPG 1800.

Example 2

It is difficult to dispense a 300,000 IU/ml procaine benzylpenicillin suspension because foaming is excessive. The suspension has been increased in volume by the foam and no longer fits in the injection vials intended for primary packaging. Addition of only 0.001% of PPG 1800 counteracts foam formation, as shown by the table below:

Table

Suspension	Density [g/ml]	
	2 minutes after shaking	60 minutes after shaking
without PPG 1800	1.012	1.00
addition of 0.001% PPG 1800	1.041	1.055
addition of 0.01% PPG 1800	1.053	1.058

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A liquid pharmaceutical formulation which is capable of being used for parenteral administration which contains ethylene oxide/propylene oxide block copolymers for controlling foam and a cephalosporin derivative or a penicillin derivative.

2. A liquid pharmaceutical formulation which is capable of being used for parenteral administration which contains polyethylene/polypropylene glycol 1800 for controlling foam in liquid pharmaceutical formulations and a cephalosporin derivative or a penicillin derivative.

3. A liquid pharmaceutical formulation as claimed in claim 1 or 2 wherein the formulation contains cefpirom.

4. A liquid pharmaceutical formulation as claimed in claim 1 or 2, wherein the formulation contains procaine benzylpenicillin.

5. A liquid pharmaceutical formulation as claimed in claim 1, wherein the concentration of ethylene oxide/propylene oxide is between 0.1 to 0.00001% by weight.

6. A liquid pharmaceutical formulation as claimed in claim 1, wherein the concentration of ethylene oxide/propylene oxide is between 0.01 to 0.0001% by weight.

7. A liquid pharmaceutical formulation as claimed in claim 2, wherein the concentration of polyethylene/polypropylene glycol 1800 is between 0.1 to 0.00001% by weight.

8. A liquid pharmaceutical formulation as claimed in claim 2, wherein the concentration of

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polyethylene/polypropylene glycol 1800 is between 0.01 to 0.0001% by weight.

9. A process for the preparation of a liquid pharmaceutical formulation as claimed in claim 1, which comprises application of an ethylene oxide/propylene oxide block copolymer to the solid active compound, or impregnation of the latter with it and subsequent dissolution in a suitable solvent, or comprises dissolution of the active compound in a solvent in the presence of an ethylene oxide/propylene oxide block copolymer.

10. The process as claimed in claim 9, wherein the ethylene oxide/propylene oxide block copolymer is polyethylene/polypropylene glycol 1800.

11. The process as claimed in claim 9 or 10, wherein the pharmaceutical formulations contain cefpirom.

12. The process as claimed in claim 9 or 10, wherein the pharmaceutical formulations contain procaine benzyl-penicillin.

13. The process as claimed in claim 9, wherein the concentration of the ethylene oxide/propylene oxide block copolymer is between 0.1 to 0.00001% by weight.

14. The process as claimed in claim 9, wherein the concentration of ethylene oxide/propylene oxide block polymer is between 0.01 to 0.0001% by weight.

15. The process as claimed in claim 10, wherein the concentration of the polyethylene/polypropylene glycol 1800 is between 0.1 to 0.0001% by weight.

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16. The process as claimed in claim 10, wherein the concentration of the polyethylene/polypropylene glycol 1800 is between 0.01 to 0.0001% by weight.

17. The use of ethylene oxide/propylene oxide block copolymers for controlling foam in liquid pharmaceutical formulations which are capable of being used for parenteral administration and which contain a cephalosporin derivative or a penicillin derivative.

18. The use of polyethylene/polypropylene glycol 1800 for controlling foam in liquid pharmaceutical formulations which are capable of being used for parenteral administration and which contain a cephalosporin derivative or a penicillin derivative.

19. The use of ethylene oxide/propylene oxide block copolymers for controlling foam in liquid pharmaceutical formulations which are capable of being used for parenteral administration and which contain cefpirom.

20. The use of ethylene oxide/propylene oxide block copolymers for controlling foam in liquid pharmaceutical formulations which are capable of being used for parenteral administration and which contain procaine benzylpenicillin.

21. The use as claimed in any one of claims 17 to 20, wherein the ethylene oxide/propylene oxide is present in a concentration of 0.1 to 0.00001.

22. The use as claimed in any one of claims 17 to 20 wherein the ethylene oxide/propylene oxide is present in a concentration of 0.01 to 0.0001% by weight.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente